STRUCTURE-TOXICITY STUDY OF SOME PYRETHROIDAL ESTER INSECTICIDES

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INTRODUCTION

- Pyrethroids constitute one of the most widely used classes of insecticides worldwide, having the following characteristics [1]: quick knock-down effect against insects, efficacy against insects with organophosphorus and/or carbamate-resistant strains, easy decomposition in the environment and low mammalian toxicity

- Although the specific mechanism of activity is uncertain, pyrethroids act primarily on the nervous system [2], on a variety of putative biochemical and physiological target sites, four of which merit consideration as sites of toxic action: voltage-sensitive sodium, calcium and chloride channels, and peripheral-type benzodiazepine receptors [3].

[1]. Y. Katsuda, *Pestic. Sci*., 1999, *55*, 775-782.
[2]. A. Anadón, M.R. Martínez-Larranãaga, M.A. Martínez, *Vet. J.*, 2009, *182*, 7–20.
[3]. D. M. Soderlund, J. M Clark, L. P. Sheets, L. S. Mullin, V. J. Piccirillo, D. Sargent, J. T. Stevens, M. L. Weiner, *Toxicology*, 2002, *171(1)*, 3–59

AIM:

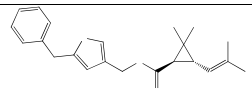
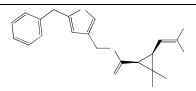
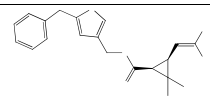
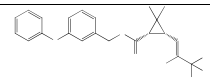
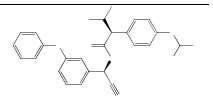
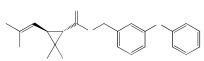
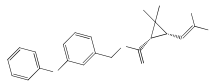
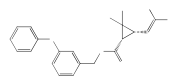
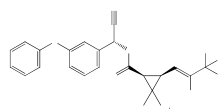
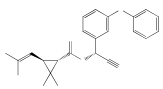
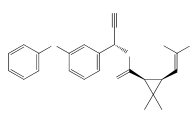
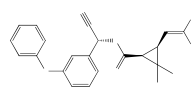
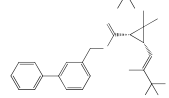
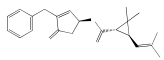
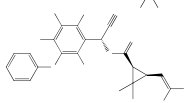
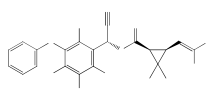
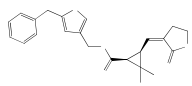
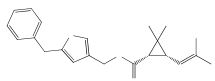
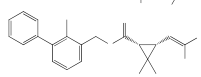
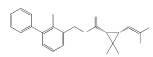
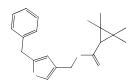
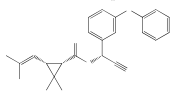
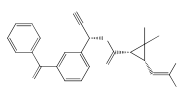
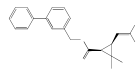
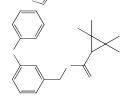
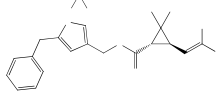
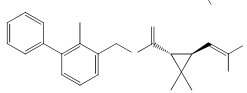
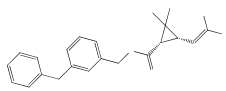
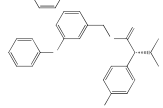
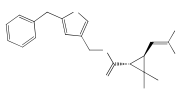
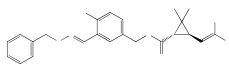
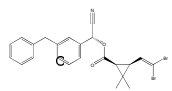
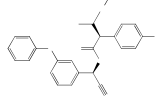
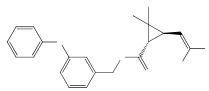
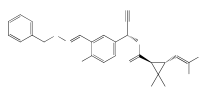
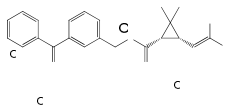
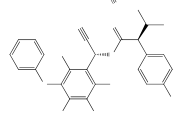
- Toxicity of 37 pyrethroidal esters (Table 1), expressed by the logarithm of LD_{50} values, measured against a susceptible strain of housefly (*Musca domestica*) was studied by multiple linear regression (MLR).

- Stereoisomers selected according to the literature [4] were modeled by conformational analysis performed by molecular mechanics calculations. Structural descriptors of the title compounds calculated for these isomers were correlated to the logarithm of LD_{50} values.

[4]. A. W. Farnham, B. P. S. Khambay, *Pestic. Sci.* 1995, *44*, 269-275.

METHODS

Table 1. Pyrethroidal ester structure

No	Structure	No	Structure	No	Structure	No	Structure	No	Structure
A1		E1		G1		H2		L3	
A2		E2		G2		H3			
A3		E3		G3		H5			
A11		E4		G4		I1			
B1		E5		G5		J1			
B3		E10		G6		J2			
C1		F5		G7		K2			
D1		F12		G8		K3			
D2		F13		G9		K4			

METHODS

- ***Definition of target property and molecular structures***

- **Experimental LD_{50} values of 37 pyrethroidal ester derivatives have been previously [4] measured against a susceptible strain of housefly (*Musca domestica*). Their logarithm was considered as dependent variable.**

- **Starting structures were first built by the Marwin Sketch [5] software and then conformational analysis was performed by the OMEGA [6] program.**

[5]. Marwin Sketch 6.0, 2013, ChemAxon, http://www.chemaxon.com

[6]. OMEGA (version 2.4.6), OpenEye Science Software, Santa Fe, USA, 2010), http://www.eyesopen.com, 2010

METHODS

- Compound descriptors were calculated by several programs: Dragon (Dragon Professional 5.5/2007, Talete S.R.L., Milano, Italy), Instant JChem (Instant JChem v. 6.0, Chemaxon Ltd., Budapest, Hungary) and EPI Suite™ (US EPA. [2012]. Estimation Programs Interface Suite™ for Microsoft® Windows, v. 4.11. United States Environmental Protection Agency, Washington, DC, USA.)

- Multiple linear regression (MLR) analysis [7] has been applied after variable selection carried out by the genetic algorithm included in the QSARINS v. 1.2 program [8].

[7]. S. Wold, W.J. Dunn III, *J. Chem..Inf. Comput. Sci.* 1983, *23*, 6-13.

[8]. N. Chirico, E. Papa, S. Kovarich, S. Cassani, P. Gramatica, *QSARINS, software for QSAR MLR model development and validation. 2012, QSAR Res. Unit in Environ. Chem. and Ecotox., DiSTA, University of Insubria, Varese, Italy. http://www.qsar.it.*

METHODS

- ***Model validation***

  - **The leave-one-out cross-validation procedure was employed for internal validation, the over fitting of data and model applicability was controlled by comparing the root-mean-square errors (RMSE) of training and validation sets and the predictive power of the model by the concordance correlation coefficient (CCC) [9].**

  - **Y-scrambling was used to check the model robustness and predictive power.**

  - **The Multi-Criteria Decision Making (MCDM) [16] was employed to summarize the performances of a certain number of criteria simultaneously**

[9]. N. Chirico, P. Gramatica, *J. Chem. Inf. Model.* 2011, *51*, 2320-2335.
[10]. H.R. Keller, D.L. Massart, J.P. Brans, *Chemom. Int.Lab. Syst*. 1991, *11*, 175-189.

RESULTS AND DISCUSSION

Table 2. MLR statistical results for the training , cross-validated and test sets

Model	Equation	R^2	Q^2	R^2_{adj}	SEE	RMSEtr	RMSEex	K_{XX}	ΔK	CCCtr	CCCex	MCDM all	R^2_{LMO}	Q^2_{LMO}	R^2Y_{scr}	Q^2Y_{scr}
1	$\log LD_{50} = -0.35(\pm 0.22) - 0.99(\pm 0.47)EEig02d - 0.55(\pm 0.31)BEHm3 + 0.62(\pm 0.32)BELm8 - 1.92(\pm 0.76)KOAWIN\log Kaw$	0.857	0.789	0.828	0.252	0.225	0.231	0.209	0.151	0.923	0.812	0.794	0.860	0.860	0.17	-0.32
2	$\log LD_{50} = -0.54(\pm 0.24) - 0.97(\pm 0.44)EEig04d + 0.44(\pm 0.30)nCp - 2.06(\pm 0.82)KOAWIN\log Kaw$	0.759	0.668	0.724	0.319	0.292	0.222	0.377	0.101	0.863	0.808	0.742	0.761	0.761	0.13	-0.25
3	$\log LD_{50} = -0.41(\pm 0.25) - 0.79(\pm 0.37)EEig02d - 0.74(\pm 0.30)MW + 0.52(\pm 0.27)BELm8 - 1.83(\pm 0.72)KOAWIN\log Kaw$	0.834	0.756	0.800	0.271	0.243	0.258	0.261	0.148	0.909	0.769	0.754	0.840	0.840	0.17	-0.33

*** R^2 – correlation coefficient, Q^2 – leave-one-out 'crossvalidated r2', R^2_{adj}- adjusted R^2, SEE – standard error of estimates, RMSE - root mean squared error, MAE - mean absolute error, CCC - concordance correlation coefficient, for the training (tr), and test (ex) sets; MCDM all - Multi-Criteria Decision Making calculated for fitting cross-validation and external validation; R^2_{LMO} and Q^2_{LMO} – leave many-out correlation coefficient and cross-validation coefficients; R^2Y_{scr} and Q^2Y_{scr}-Y scramble correlation and cross-validation coefficients; EEig02d-Eigenvalue 02 from edge adj. matrix weighted by dipole moments; BEHm3-highest eigenvalue n. 3 of Burden matrix / weighted by atomic masses; BELm8-lowest eigenvalue n. 8 of Burden matrix / weighted by atomic masses; KOAWIN Log Kaw–air-water partition coefficients; nCp-number of terminal primary C(sp3); MW-molecular weight**

RESULTS AND DISCUSSION

- The dataset was divided in training and a randomly selected (25% of the total number of compounds) test set. Compounds: C1, D1, G1, H3 and L3 were included in the test set.

- Seven outliers (compounds A1, B1, B3, F12, F13, G2 and H5) were found and removed from the final MLR models.

- The MLR models are completely satisfactory in the fitting, but have modest predictive power.

- Model 1 (considered best) is stable and internally predictive, not obtained by chance.

RESULTS AND DISCUSSION

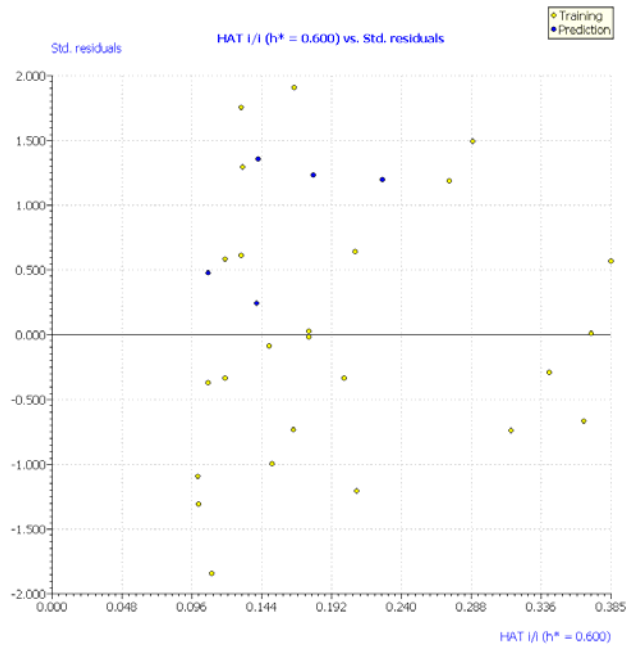


Figure 1. Williams plot – predicted by fitting for model 1

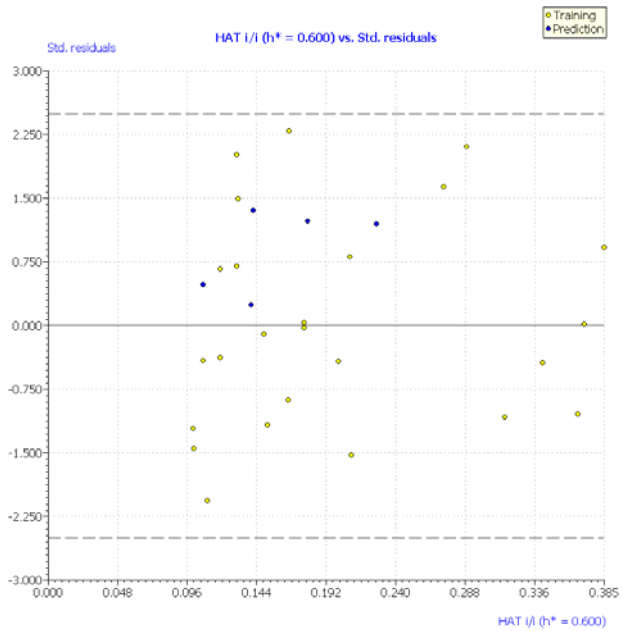


Figure 2. Williams plot – predicted by leave-one-out (LOO) for model 1

RESULTS AND DISCUSSION

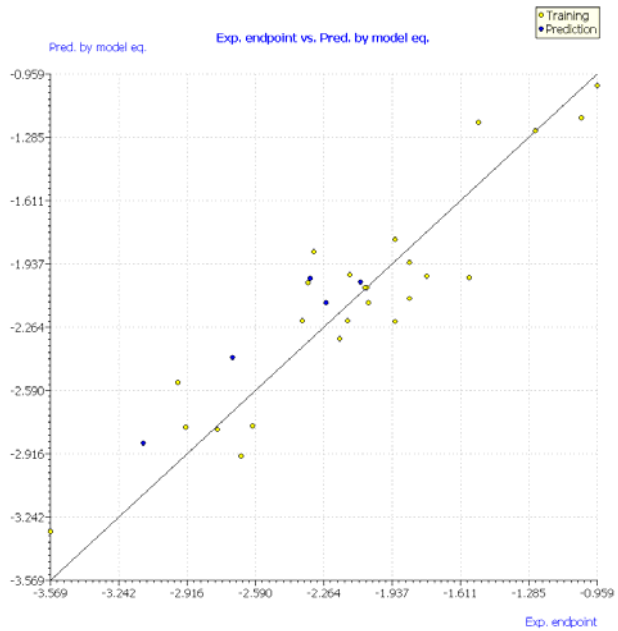


Figure 3. Experimental versus $logLD_{50}$ values predicted by fitting for model 1

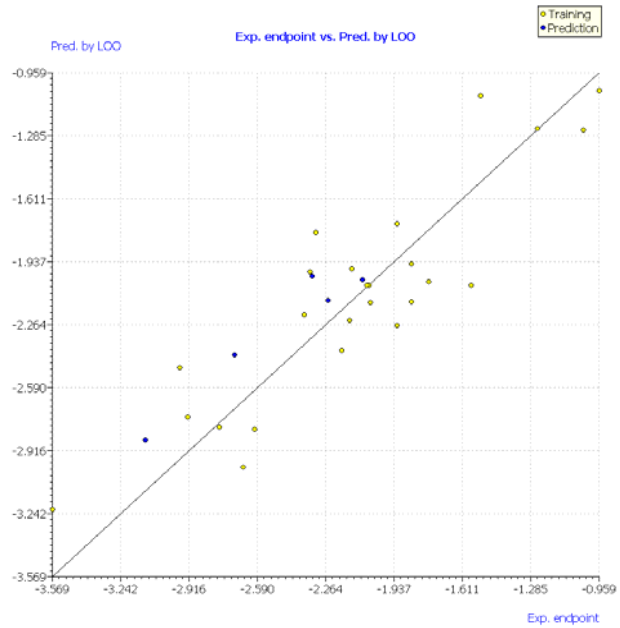


Figure 4. Experimental versus $logLD_{50}$ values predicted by LOO for model

CONCLUSIONS

- The obtained MLR models are satisfactory in the fitting, but have modest predictive power.
- The presence number of terminal primary C(sp3) group is favorable for low toxicity.
- High values of air-water partition coefficients and of molecular weight can be associated with high toxicity of the title compounds.

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